Flecainide induced peripheral neuropathy

Drs JACKIE PALACE (Department of Neurology Guy's Hospital), RASHMI SHAH (Medicines Control Agency), and CHRIS CLOUGH (Department of Neurology, Brook General Hospital, London) write: The non-cardiac side effects of class 1 antiarrhythmic agents, including flecainide, predominantly affect the central nervous system, producing symptoms such as dizziness, visual disturbances, headache, fatigue, tremor, nervousness paraesthesia, hypoaesthesia, and weakness.¹ We describe a patient who developed peripheral neuropathy after long-term flecainide treatment which regressed after withdrawal of the drug.

A 51 year old man had suffered from paroxysmal supraventricular tachycardia for 13 years, having been treated unsuccessfully with β blockers and verapamil. Flecainide 100 mg three times a day was started; he was taking no other medication. His renal and hepatic function were normal and he had been otherwise well. Two and a half years later he presented with a two month history of progressive paraesthesiae starting in his hands and feet. Examination showed a glove and stocking type of sensory loss. His tendon reflexes were diminished in the arms and absent in the legs. Plantar responses were flexor and motor power was full.

Nerve conduction studies showed reduction in nerve action amplitudes with normal conduction velocities, suggesting an axonal, mainly sensory polyneuropathy (see table). All blood tests including erythrocyte sedimentation rate; measurement of γ -glutamyl transferase, glucose, B12 and folate, serum lead, autoantibodies, γ -globulins; *Treponema pallidum* haemagglutination assay; protein electrophoresis; thyroid function tests; and *Mycoplasma* and *Borrelia* titres were normal, as were urinary concentrations of porphyrins and the cerebrospinal fluid. Over the next four weeks the sensory

symptoms and signs progressed. Flecainide was withdrawn and amiodarone started. Within three months the patient improved dramatically, until he had only mild residual hypoaesthesia in his hands and feet and all his limb reflexes had returned. Repeat nerve conduction studies showed improvement in both sensory and motor action potential amplitudes consistent with a resolving axonal sensory-motor neuropathy (table). Nine months later he still had some mild sensory loss.

The Committee on Safety of Medicines has received four other reports of possible peripheral neuropathies associated with flecainide and three of patients in whom pre-existing neuropathy was aggravated by flecainide. There was no obvious age, sex, or dose related predisposition and the onset of symptoms ranged from three days to 12 months after flecainide was started. The neuropathy did not resolve in all cases. Metabolic elimination by hepatic oxidation of many drugs is genetically controlled.² Poor metabolisers (8-9% of the population) have a diminished capacity to eliminate many drugs, including flecainide,³ by oxidative metabolism. A genetically determined poor drug oxidation ability was associated with the high incidence of severe peripheral and central neuropathies with perhexiline (a drug with similar properties to flecainide).⁴ Poor metabolisers may also be at greater risk of developing flecainide-induced ventricular tachycardias.⁵ The possibility that neuropathy may also occur in patients with defective flecainide oxidation warrants investigation.

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Diarrhoea during treatment with clozapine: association with lymphocyte count

Drs R J HARVEY, T BULLOCK, and S A MONTGOMERY (Academic Department of Psychiatry, St Mary's Hospital, London W2 1NY) write: We report three cases of severe diarrhoea occurring during treatment with clozapine, a novel antipsychotic drug with a high incidence of side effects. Because agranulocytosis occurs in 2-3% of patients (with a mortality of up to 35%), the drug can be dispensed only if regular blood count monitoring is performed by the pharmaceutical company. We describe changes in the blood count coinciding with the onset of the diarrhoea. The cases occurred at different times, and there were no other cases of diarrhoea on the unit. All patients had treatment resistant schizophrenia and no other medical problems.

Case 1—On the 13th day of treatment with clozapine 200 mg alone this 60 year old white woman developed severe diarrhoea with faecal incontinence, pyrexia, hypotension, acute renal impairment (serum creatinine 140 mmol/l (normal 60-125) mmol/l), and a drop in the lymphocyte count to $0.8 \times 10^9/l$ (normal $1.5-4.0$). Treatment was discontinued and no infective cause found. Clozapine 275 mg/day was restarted after 21 days. Nine weeks later treatment was halted when agranulocytosis developed (neutrophil count $0.42 \times 10^9/l$ (normal $2.0-7.5$), total white cell count $1.48 \times 10^9/l$ (normal $4.0-11.0$)).

Case 2—A 47 year old white man was taking clozapine 200 mg daily with diazepam, promethazine, and procyclidine. At week 6 profuse diarrhoea developed, associated with incontinence, hypotension, acute renal impairment (serum creatinine 300 mmol/l , potassium 7.0 mmol/l (normal $3.5-5.0$)), and a fall in the lymphocyte count to $0.64 \times 10^9/l$. Clozapine was discontinued and no infective cause was found in the stool. Blood cultures grew *Escherichia coli*, which was treated with intravenous ceftazidime and metronidazole. A rectal biopsy specimen suggested pseudomembranous colitis, which was also shown by barium enema. *Clostridium difficile* was not isolated from stool samples, though a course of vancomycin was given. Subsequent sigmoidoscopy and barium enema showed normal findings.

Case 3—A 26 year old Afro-

Caribbean man receiving clozapine 450 mg and sulpiride 400 mg daily developed severe diarrhoea in the ninth month of treatment; he had faecal incontinence but was otherwise well. The clozapine was stopped and the diarrhoea settled. No infective cause was found. On rechallenge with clozapine he developed recurrent neutropenia and treatment was discontinued.

Diarrhoea occurring during treatment with clozapine is a side effect not previously described, although seven other cases have been reported to the pharmaceutical company (Sandoz, UK, July 1992) and the Committee on Safety of Medicines has received nine reports of diarrhoea, two of faecal incontinence, and two of pseudomembranous colitis. In two of our cases there was an associated drop in the lymphocyte count. On rechallenge one patient developed agranulocytosis and one a recurrent neutropenia.

How clozapine affects the white cell population is unknown, although an immunological origin is suspected. Since the first reports of agranulocytosis in 1975 it has been recognised that clozapine affects not only neutrophils but may cause thrombocytopenia, eosinopenia, pancytopenia and leukaemia.² There have been no previous accounts of the effects of clozapine on lymphocytes. Case 1 shows a clear relation between falling lymphocyte and neutrophil counts, reversed by stopping treatment.

The mechanism of the diarrhoea is also unclear. A direct effect of clozapine on the bowel is unlikely, as in two cases rechallenge did not cause further diarrhoea. Viral infection reduces the lymphocyte count but does not explain the subsequent pancytopenia in two of the patients. However, as gut immunity to both bacteria and viruses seems principally dependent on the generation of secretory IgA by plasma cells, a causal connection between the lymphopenia and the diarrhoea is possible. The *E coli* grown from the blood of one of the patients would support a possible bacterial causation for the diarrhoea, with the deficit of IgA production increasing the invasiveness of the *E coli*. Depression of the lymphocyte count may be an early immunosuppressive effect of the clozapine in patients who subsequently develop agranulocytosis. Our findings have implications for the monitoring service: should the counts for other white cell subgroups be used in determining the patient's treatment and should the development of an intercurrent illness be an indication for more frequent monitoring?

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Nerve conduction studies of patient while taking flecainide and four months after withdrawal

Nerve	Stimulus	Amplitude (mV)			Conduction velocity (m/s)		
		On flecainide	After withdrawal	Normal	On flecainide	After withdrawal	Normal
Left tibial	Ankle	4.5	<i>Motor</i> 5.92	> 4	Not obtainable	49	> 40
	Popliteal fossa	Absent	2.86	> 4			
Right median	Wrist	Absent	3.71	> 4			
Right ulnar	Wrist	Absent	3.84	> 4			
Right sural	Calf	Absent	<i>Sensory</i> 6.67	> 9.0	Not obtainable 40	39	> 40
			1.35	7.76		> 9.0	39
Left sural	Calf	1.35	7.76	> 9.0		39	> 40
Right median	2nd digit	4.60	5.29	> 14.0	54	54	> 50
Left median	2nd digit	3.88	10.18	> 14.0	59	54	> 50
Left ulnar	5th digit	1.92	5.31	> 9.0	50	50	> 50